Pharmacokinetics, Pharmacodynamics, and Safety of Plozasiran in Subjects with Renal or Hepatic Impairment

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Disclosure Slide

	No, nothing to disclose
x	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
Arrowhead Pharmaceuticals					x	x	x	

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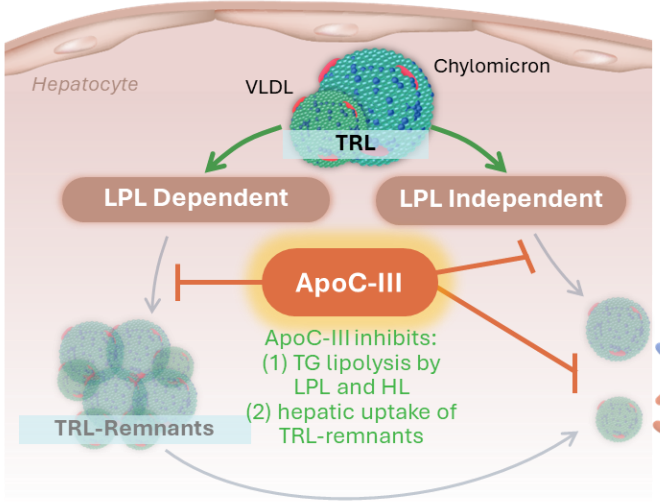
Plozasiran is a siRNA Targeting Hepatic APOC3

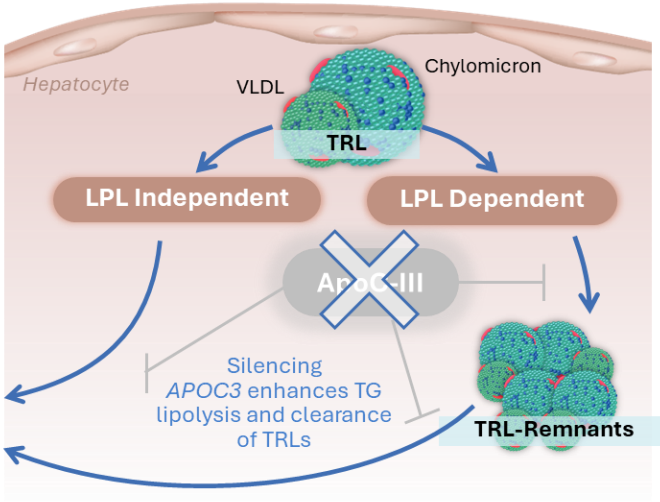
CHYLOMICRONEMIA[1,2]

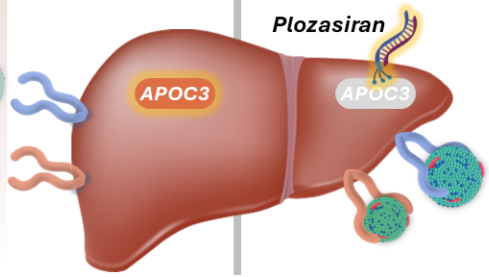
ApoC-III inhibits lipolysis and hepatic clearance of TRLs, increasing TGs



PLOZASIRAN[2]

Silencing of APOC3 enhances lipolysis and hepatic clearance of TRLs, reducing TGs





APOC3, apolipoprotein C3 gene; ApoC-III, apolipoprotein C-III protein; FCS, Familial Chylomicronemia Syndrome; HL, hepatic lipase; LPL, lipoprotein lipase; siRNA, small interfering RNA; TG, triglyceride; TRL, triglyceride-rich lipoprotein; VLDL, very-low-density lipoprotein.

1. Van Zwol W, et al. *J Clin Med*. 2019;8(7):1085. 2. Ballantyne CM, et al. *New Engl J Med*. 2024;391(10):899-912

Study Rationale

- Plozasiran (Redemplo®) is FDA approved and has received a positive CHMP opinion as an adjunct to diet to reduce TGs in adults with FCS and is in development for the treatment of sHTG
- Hypertriglyceridemia exists frequently with comorbid conditions, including hepatic steatosis, diabetes, or chronic kidney disease[1]
- Prevalence of hepatic complications such as hepatosplenomegaly and hepatic steatosis (2-3 times) is higher in patients with FCS and sHTG versus the general population[2]
- A recent study showed high rates of renal abnormalities in a cohort of chylomicronemia patients (N=84) including:[3]
  - Reduced eGFR (<90 mL/min): 49%
  - Hyperfiltration: 41%
  - Proteinuria: 35%

Study objective: To assess the impact of hepatic or renal impairment on the PK, PD, and safety of single-dose 25-mg plozasiran

CHMP, Committee for Medicinal Products for Human Use; EMA, European Medicines Agency; FDA, US Food & Drug Administration; eGFR, estimated glomerular filtration rate; FCS, Familial Chylomicronemia Syndrome; PD, pharmacodynamics; PK, pharmacokinetics; TG, triglyceride; sHTG, severe hypertriglyceridemia.

1. Gurevitz C, et al. *JACC Adv*. 2024;3(5):100932. 2. Ariane De Villers-Lacasse et al. J.clin.Lipid. 2023;17(4) 475-482.
3. D'Erasmo L, et al. *Atherosclerosis*. 2026;413:1020621.

Study Cohorts

- AROAPOC3-1004 was an open-label, parallel-group study that enrolled adult participants into 4 cohorts:

Moderate Renal Impairment (n=8)
eGFR: 30–60 mL/min, with 3 subjects having a baseline eGFR: 30–45 mL/min

Severe Renal Impairment (n=8)
eGFR< 30 mL/min not receiving dialysis

Moderate Hepatic Impairment (n=9)
Child-Pugh Class B

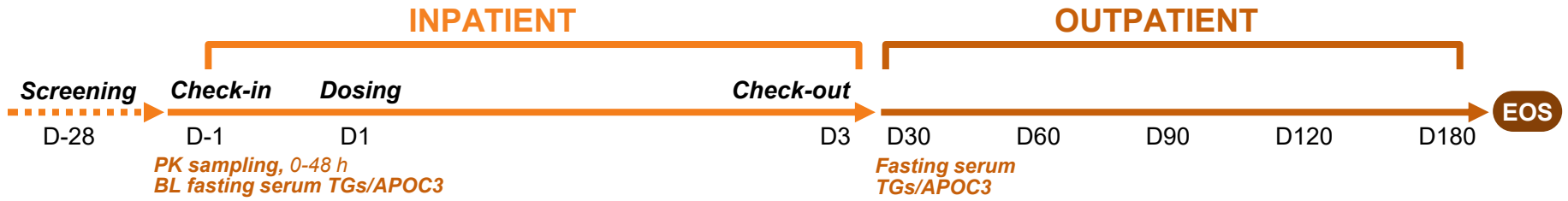
Enrolled later to match demographics

Controls (n=12)
Normal renal (eGFR≥ 90/min) and hepatic function

- Subgroup 1: Renal Matched Controls (n=8)
- Subgroup 2: Hepatic Matched Controls (n=8)

eGFR, estimated glomerular filtration rate; Child-Pugh Class B score is a system for assessing the prognosis of chronic liver disease; it provides a forecast of the increasing severity of liver disease .

Study Design



Plozasiran 25 mg SC

COHORT 1
Normal Renal & Hepatic Functions

COHORT 2
Moderate Renal Impairment

COHORT 3
Severe Renal Impairment

COHORT 4
Moderate Hepatic Impairment

APOC3, apolipoprotein 3; BL, baseline; EOS, end of study; SC, subcutaneous; TG, triglycerides.

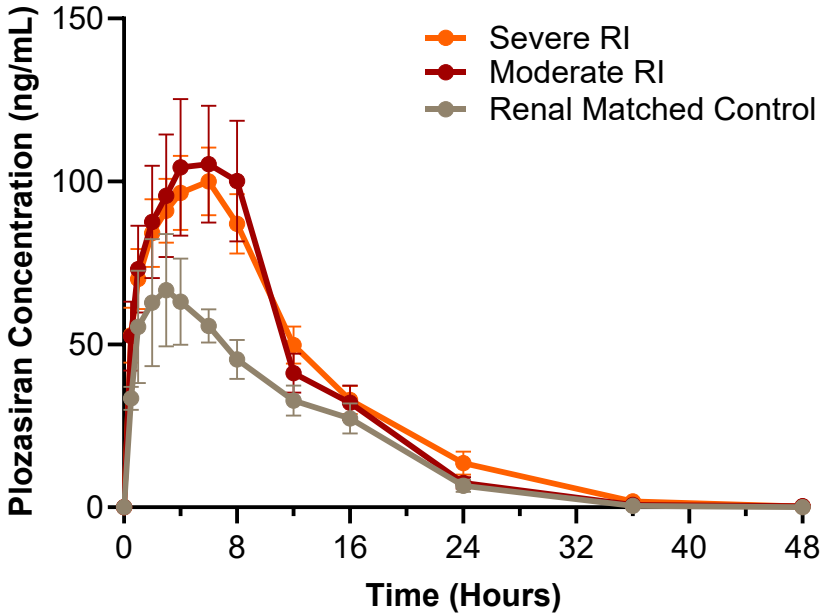
Baseline Demographic Characteristics

	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)	Renal Matched Controls (n=8)	Moderate Hepatic Impairment (n=9)	Hepatic Matched Controls (n=8)
Age (years), Mean (SD)	63.1 (7.38)	65.6 (12.6)	60.0 (3.36)	61.9 (9.53)	57.3 (4.20)
Race, n, (%)					
White	5 (62.5)	4 (50.0)	4 (50.0)	8 (88.9)	7 (87.5)
Black	2 (25.0)	4 (50.0)	4 (50.0)	0	1 (12.5)
Other	1 (12.5)	0	0	1 (11.1)	0
Males, n, (%)	2 (25.0)	2 (25.0)	2 (25.0)	6 (66.7)	5 (62.5)
Weight (kg), Mean (SD)	89.6 (17.1)	88.1 (12.5)	92.3 (7.18)	87.7 (15.0)	91.0 (5.10)
BMI (kg/m^2), Mean (SD)	32.5 (5.02)	32.5 (5.70)	33.9 (2.67)	32.5 (5.01)	32.0 (3.74)
Triglycerides (mmol/L), Median (Q1, Q3)	1.03 (0.847, 2.29)	1.35 (1.04, 1.72)	1.29[a] (0.824, 1.37)	1.43[b] (1.03, 4.41)	1.29 (0.909, 1.41)

[a] n=7, one subject was excluded in TG analysis for low baseline TG values and no observable TG reduction
[b] n=7, two subjects were excluded in TG analysis for low baseline TG values and no observable TG reduction

BMI, body mass index; SD, standard deviation; TG, triglycerides

Moderate Increase in Plozasiran Exposure with Renal Impairment

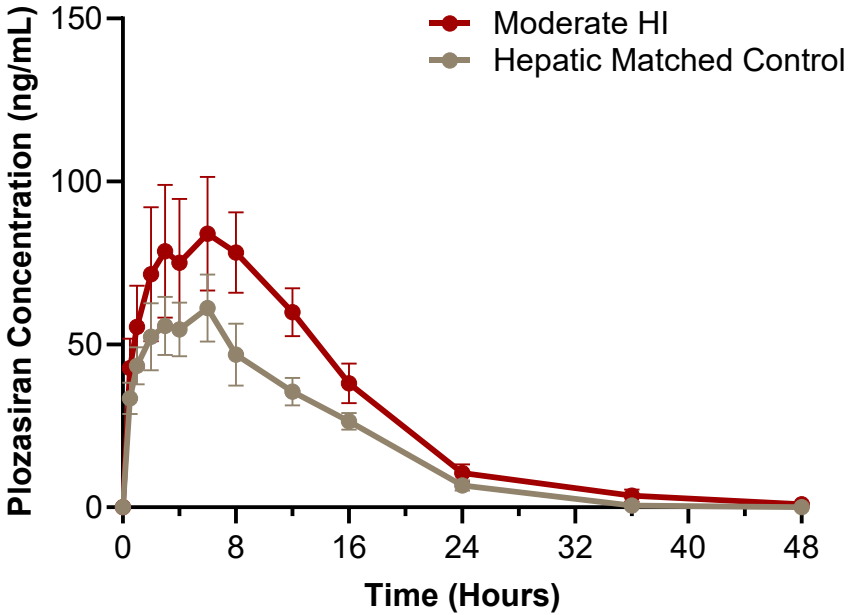


Cohort	Parameter	Geometric Mean Ratio (90% CI)
Moderate RI vs Matched Control	C_{max}	1.67 (1.13–2.47)
	AUC_{0-t}	1.50 (1.18–1.92)
	AUC_{0-inf}	1.49 (1.16–1.92)
Severe RI vs Matched Control	C_{max}	1.56 (1.05–2.30)
	AUC_{0-t}	1.62 (1.27–2.06)
	AUC_{0-inf}	1.59 (1.24–2.04)

- Mean renal clearance (CL_R) was reduced from 2.82 L/h in matched controls to 0.939 L/h and 0.420 L/h in moderate and severe RI cohorts, respectively

CI, confidence interval; RI, renal impairment.

Moderate Increase in Plozasiran Exposure with Hepatic Impairment



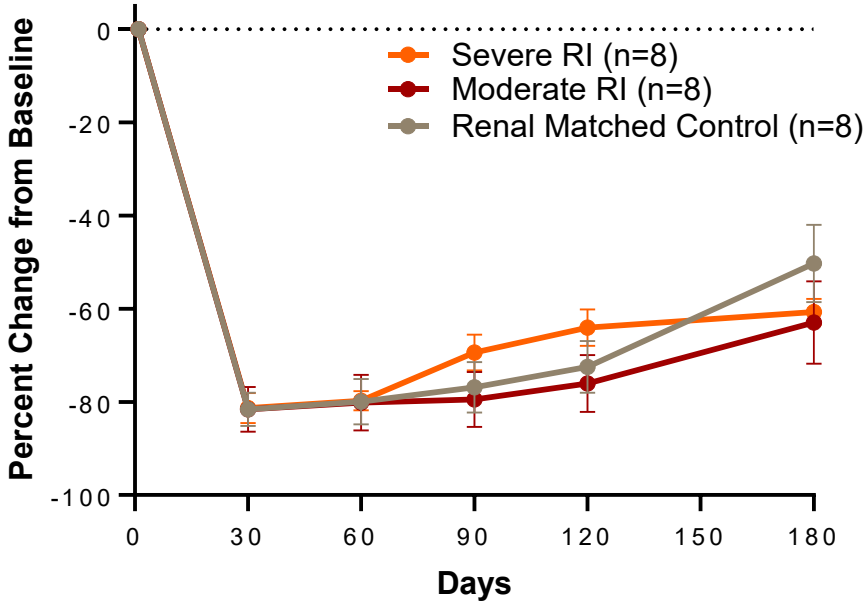
Cohort	Parameter	Geometric Mean Ratio (90% CI)
Moderate HI vs Matched Control	C_{max}	1.33 (0.880–2.02)
	AUC_{0-t}	1.51 (1.13–2.01)
	AUC_{0-inf}	1.42 (1.05–1.94)

- Geometric mean renal clearance (CL_R) was comparable between cohorts, with values of 2.60 L/h in matched controls and 2.45 L/h in the moderate HI cohort

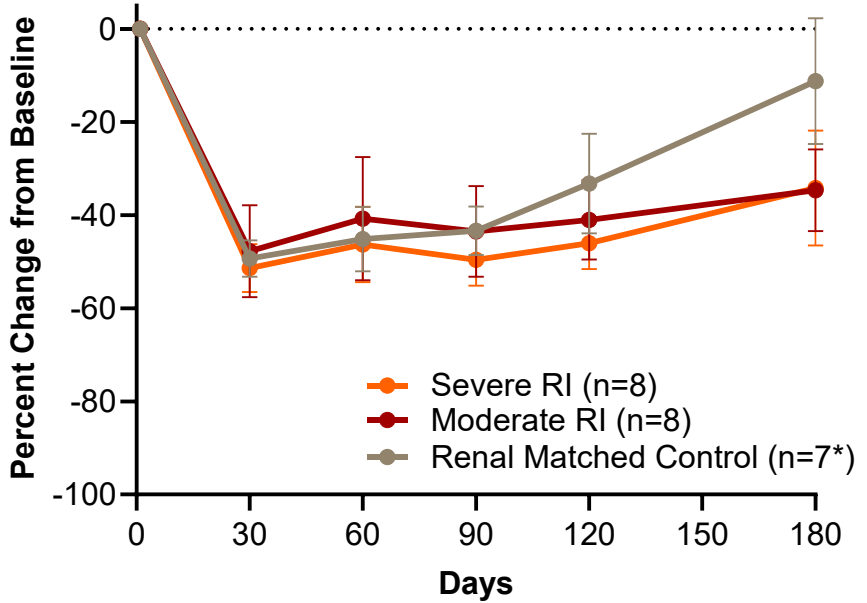
CI, confidence interval; HI, hepatic impairment.

Pharmacodynamics Were Not Meaningfully Altered with Moderate or Severe Renal Impairment

Percent Change in Serum APOC3



Percent Change in Serum TGs

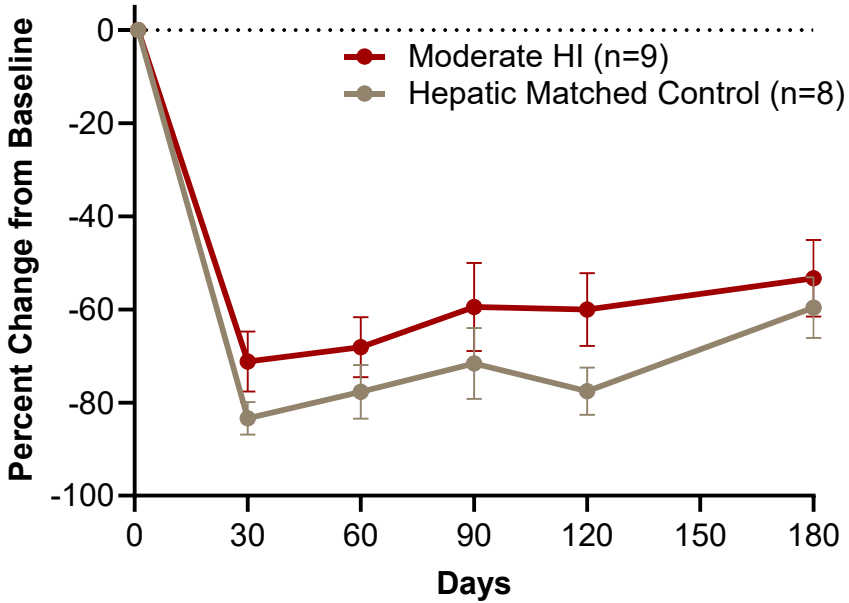


- Similar mean maximum percent reductions in serum APOC3 (−83%) and TGs (−52 to −57%) between moderate and severe renal impairment and matched healthy cohorts

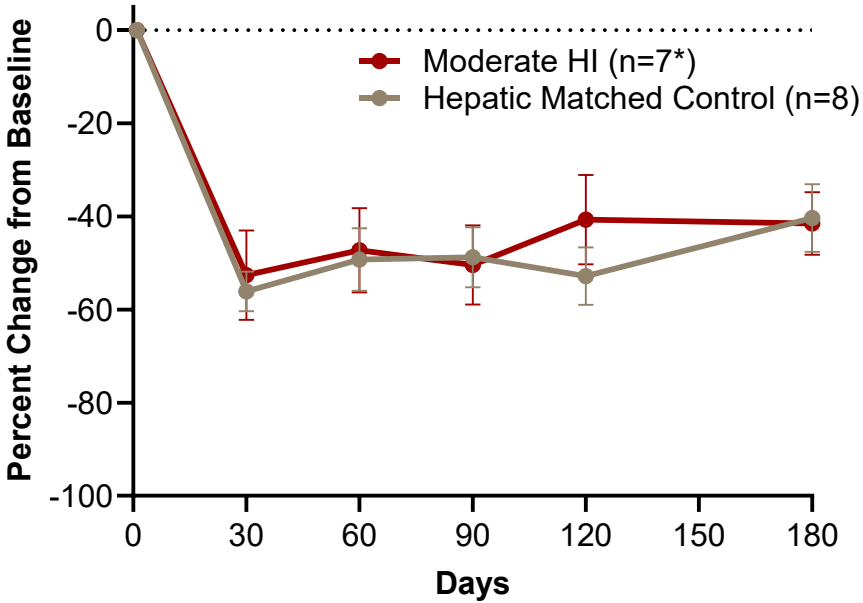
*1 subject in the renal matched cohort with low BL TG value (0.28 mmol/L) and no observable TG reduction was excluded from the TG response analysis because further decrease from a very low TG BL may not be physiologically feasible RI, renal impairment; TGs, triglycerides.

Pharmacodynamics Were Not Meaningfully Altered with Moderate Hepatic Impairment

Percent Change in Serum APOC3



Percent Change in Serum TGs



- Similar mean maximum APOC3 reduction in moderate HI subjects (−76%) compared to matched controls (−86%); consistent maximum TG reductions between HI and control groups (−58%)

*2 subjects in the moderate HI cohort with low BL TG values (0.28–0.46 mmol/L) and no observable TG reduction were excluded from the TG response analysis because further decrease from a very low TG BL may not be physiologically feasible. HI, hepatic impairment; TGs, triglycerides.

Plozasiran was Well-Tolerated, with No Serious TEAEs* or TEAEs Leading to Discontinuation

Subjects, n (%)	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=16)	Renal Matched Controls (n=8)	Moderate Hepatic Impairment (n=9)	Hepatic Matched Controls (n=8)
≥1 TEAE	2 (25.0)	1 (12.5)	0	6 (66.7)	0
TEAEs leading to discontinuation	0	0	0	0	0
Serious TEAEs*	1 (12.5)†	1 (12.5)‡	0	0	0
Serious TEAEs Related to Study Drug	0	0	0	0	0

Laboratory assessments showed no evidence of renal or hepatic injury

*None of the serious TEAEs were related to plozasiran; †Gastroenteritis; ‡Peripheral edema. TEAE, treatment-emergent adverse event.

No Renal/Hepatic TEAEs were Reported

Subjects, n%	Moderate Renal Impairment (n=8)	Severe Renal Impairment (n=8)	Renal Matched Controls (n=8)	Moderate Hepatic Impairment (n=9)	Hepatic Matched Controls (n=8)
Headache	1 (12.5)	0	0	2 (22.2)	0
Acute myocardial infarction	1 (12.5)	0	0	0	0
Gastroenteritis*	1 (12.5)	0	0	0	0
Hypertension	1 (12.5)	0	0	0	0
Peripheral edema	0	1 (12.5)	0	0	0
Systemic inflammatory response syndrome*	1 (12.5)	0	0	0	0
Arthralgia	0	0	0	1 (11.1)	0
Diabetic neuropathy	0	0	0	1 (11.1)	0
Diarrhea	0	0	0	1 (11.1)	0
Injection site erythema	0	0	0	1 (11.1)	0
Lipase increased	0	0	0	1 (11.1)	0
Urinary tract infection	0	0	0	1 (11.1)	0

*SIRS case characterized by leukocytosis and tachycardia, was assessed as secondary to gastroenteritis due to food poisoning and not related to study drug; TEAE, treatment-emergent adverse event.

Conclusions

- Despite moderate (1.3–1.7x) increases in plozasiran exposure, PD responses (APOC3 and TG reduction) were similar between control cohorts and those with moderate to severe renal or moderate hepatic impairment
- Plozasiran was generally safe and well-tolerated, with no renal or hepatic TEAEs nor clinically meaningful evidence of worsening renal or hepatic function
- Together, these data support the use of plozasiran 25 mg in patients with moderate-to-severe renal impairment or moderate hepatic impairment without dose adjustment
- Future trials will help further evaluate plozasiran safety in patients with advanced liver/renal disease

TEAE, treatment-emergent adverse event; TG, triglyceride.

thank you

We would like to thank the participants and caregivers who took part in this study